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Relative differences in resting-state brain connectivity associated with long term intensive lifestyle intervention

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ABSTRACT

A number of studies have reported that type 2 diabetes mellitus (T2DM) is associated with alterations in resting-state activity and connectivity in the brain. There is also evidence that interventions involving physical activity and weight loss may affect brain functional connectivity. In this study, we examined the effects of nearly 10 years of an intensive lifestyle intervention (ILI), designed to induce and sustain weight loss through lower caloric intake and increased physical activity, on resting-state networks in adults with T2DM. We performed a cross-sectional comparison of global and local characteristics from functional brain networks between individuals who had been randomly assigned to ILI or a control condition of health education and support. Upon examining brain networks from 312 participants (average age: 68.8 for ILI and 67.9 for controls), we found that ILI participants (N = 160) had attenuated local efficiency at the network-level compared with controls (N = 152). Although there was no group difference in the network-level global efficiency, we found that, among ILI participants, nodal global efficiency was elevated in left fusiform gyrus, right middle frontal gyrus, and pars opercularis of right inferior frontal gyrus. These effects were age-dependent, with more pronounced effects for older participants. Overall these results indicate that the individuals assigned to the ILI had brain networks with less regional and more global connectivity, particularly involving frontal lobes. Such patterns would support greater distributed information processing. Future studies are needed to determine if these differences are associated with age-related compensatory function in the ILI group or worse pathology in the control group.

Functional magnetic resonance imaging (fMRI) studies evaluating brain activity at rest using the blood oxygen level dependent (BOLD) technique allows identification and evaluation of several brain networks defined by synchronous activity patterns. The network of brain areas known as the default mode network (DMN), so named due to higher activity in this network when the brain is at rest, contains the posterior cingulate cortex, precuneus, medial temporal lobe, inferior parietal lobe, and medial prefrontal cortex. Alterations in brain functional architecture have been reported among adults with type 2 diabetes mellitus (T2DM). Recent studies among individuals with T2DM have found patterns of decreased functional and structural connectivity in these individuals compared with healthy controls (Zhou et al., 2010; Musen et al., 2012; Chen et al., 2014; Hoogenboom et al., 2014), particularly in the DMN. A similar trend was also discovered among obese people

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compared with healthy controls (Kullmann et al., 2012). In addition to resting-state connectivity, resting-state activity is also reduced in some brain areas in T2DM patients (Xia et al., 2013; Cui et al., 2014).

Recent short-term studies with interventions in obese and/or older individuals have shown that increased physical activities have protective effects on the brain, including increases in the volume (Erickson et al., 2011) and blood flow (Burdette et al., 2010) to the hippocampus and improved functional connectivity in the DMN (Burdette et al., 2010; Voss et al., 2010a,b; Li et al., 2014). Alterations in resting-state brain activity are also reported. Increased resting-state activity has been observed in the middle and superior frontal gyri associated with an intervention involving Tai Chi, cognitive training, and counseling (Yin et al., 2014). On the other hand, reduced resting-state activity was observed in the DMN associated with a treadmill-walking exercise intervention (McFadden et al., 2013). Less is known about whether weight loss, separate from physical activity, alters resting state brain activity. The few published results are based on small studies (Frank et al., 2014; Prehn et al., 2016).

We report findings from resting-state functional brain MRI collected from overweight and obese adults with T2DM who enrolled in a randomized controlled clinical trial of 9.8 years of intensive lifestyle intervention designed to induce and sustain weight loss. We have previously reported that this intervention was associated with improvements in brain structure: lower ischemic lesion and ventricle volumes (Espeland et al., 2016). The hypothesis framing this current manuscript is that random assignment to this long term lifestyle intervention, compared with a control condition of diabetes support and education, is associated with differences in local and global network efficiency.

1. Materials and methods

1.1. Subjects

The design and methods of the parent study, the Action for Health in Diabetes (Look AHEAD) trial, have been published previously (Ryan et al., 2003). At baseline (2001–2004), participants had T2DM, age between 45 and 76 years, body mass index $\geq$25 kg/m^2 ($\geq$27 kg/m^2 if taking insulin), HbA1c < 11%, systolic blood pressure <160 mmHg, diastolic blood pressure <100 mmHg, and triglycerides <600 mg/dl. All subjects passed a maximal graded exercise test in order to ensure that exercise could be safely prescribed. Additional eligibility criteria included run-in and an interview with a behavioralist for judging the ability of the participant to adhere to lifestyle intervention, which may have culled some with overt cognitive impairment.

A subset of participants from three Look AHEAD sites (Philadelphia, PA; Pittsburgh, PA; Providence, RI) enrolled in the Look AHEAD Brain Magnetic Resonance Imaging (Look AHEAD Brain) study in 2012–2014, an ancillary study examining brain structure and function (Espeland et al., 2016), at their 10th, 11th, or 12th anniversary from their Look AHEAD enrollment. Eligibility was limited to active participants for whom MRI was safe (e.g. metal implants and claustrophobia excluded some participants) and could be obtained (some of the largest Look AHEAD participants could not be scanned). All participants signed a separate informed consent form for the Look AHEAD Brain study, approved by local Institutional Review Boards prior to their enrollment.

1.2. Interventions

At the time of Look AHEAD enrollment, participants were randomly assigned, with equal probability, to the Intensive Lifestyle Intervention (ILI), or to the control arm referred to as Diabetes Support and Education (DSE). The ILI, which included diet modification and physical activity, was designed to induce $\geq$7% weight loss during the first year and to maintain this weight loss for the following years (Look AHEAD, 2006). ILI individuals were provided frequent group and individual treatment sessions for the study's duration, as described previously (Look AHEAD, 2006). The DSE participants were offered three group sessions each year (for the first 4 years) that provided education (but not behavioral instruction) about diet, physical activity, or social support (Wesche-Thobaben et al., 2011). Medical care for participants was provided by their personal physicians, except for temporary changes in diabetes medication to treat hypoglycemia during the intensive weight loss periods in ILI (Ryan et al., 2003). The intervention phase of Look AHEAD ended September 2012.

Intervention adherence was assessed by centrally trained staff that was masked to intervention assignment (Ryan et al., 2003). Body mass index (weight in kilograms divided by the square of height in meters) was measured annually. A maximal graded exercise test was administered at baseline and a submaximal exercise test at years 1 and 4, and on a subset of participants at year 2 (Jakicic et al., 2009). Changes in fitness at years 1 and 4 were computed as the difference between estimated metabolic equivalents (METS) when the participants achieved or exceeded 80% of age-predicted maximal heart rate or Borg Rating of Perceived Exertion of >16 at baseline and at the subsequent assessment. The Paffenbarger Physical Activity Questionnaire was used to estimate weekly minutes of moderate-to-vigorous physical activity at years 1, 4, and 8 in a subset of participants.

1.3. Brain MRI data

Each participant's brain MRI scan included structural MRI and resting-state functional MRI data. The Look AHEAD T1-weighted structural MRI was acquired with a 1 mm volumetric MPRAGE sequence (Espeland et al., 2016). The structural image was spatially normalized to the Jakob template space after skull-stripping. The Jakob template is one of the MNI (Montréal Neurological Institute) templates. The resting-state fMRI data consisted of a series of 152 scans acquired with TR = 2 s while participants rested with eyes open, fixating on a centrally located crosshair inside the MRI scanner. The fMRI frames were aligned to correct for head motion during the scan, co-registered to the participant's structural image, and spatially normalized to the MNI space. The fMRI data were then band-pass filtered (0.009–0.08 Hz) to attenuate respiration and other physiological noises. In addition, six affine transformation parameters from the alignment process, as well as the mean time courses from the brain parenchyma including all gray and white matter tissues, deep white matter, and ventricles were regressed out in order to correct further motion and physiological noises. The use of global signal regression remains a topic of research as there are mixed views on the importance of this procedure. We have chosen to use global signal regression because there is evidence that it is important for assessing regional differences and helps reduce artifacts associated with large draining veins (Hayasaka, 2013). To reduce the effects from motion artifacts, time points with a large displacement were identified. In the process known as motion scrubbing, a time point with the frame displacement (FD) greater than 0.5 was considered excessive as suggested by Power et al., and that time point as well as the one prior and the two following were removed (Power et al., 2012).

The MRI Reading Center at the University of Pennsylvania oversaw quality control of the brain MRI data collected from the three imaging sites, utilizing Siemens Tim Trio scanners. Both ADNI (Alzheimer's Disease Neuroimaging Initiative) and fBIRN (functional Biomedical Informatics Research Network) phantoms were